Section II (Remarks)

A. Summary of Amendment to the Claims

Claim 5 has been amended as set forth in the above Complete Listing of the Claims. As amended, the claims are supported by the specification and the original claims. No new matter has been added, as defined by 35 U.S.C. § 132.

Thus, upon entry of the amendments, claims 1 and 4-12 will be pending, of which claims 8 and 10 are withdrawn. Accordingly, claims 1, 4-7, 9, 11 and 12 are pending and under examination.

In view of the finality of the August 17, 2009 Office Action and to ensure substantive consideration of this response, a Request for Continued Examination is concurrently submitted herewith. Entry and consideration of the response are respectfully requested.

B. (Rejection of Claims Under 35 U.S.C. §103(a)

In the Office Action mailed August 17, 2009 the examiner maintained the rejection of claims 1 and 4-6 under 35 U.S.C. §103(a) as unpatentable over MacBeath et al., *Science*, Sept. 8, 2000, vol. 289, pp. 1760-3 (hereinafter "MacBeath") in view of U.S. Patent No. 6,335,176 (hereinafter "Inglese"). Applicants respectfully disagree.

The examiner's attention is respectfully drawn to claim 1 of the present application, from which all other pending claims depend. Claim 1 recites "[a] protein chip of a S-L-SP form…" The combination of MacBeath in view of Inglese does not make a protein chip of a S-L-SP form obvious.

The examiner states that the rejection is maintained for the reasons of record. MacBeath is not further addressed by the examiner with respect to its substantive disclosure in the Office Action mailed August 17, 2009. In the prior Office Action, the examiner had alleged that MacBeath "teaches protein microarrays…for high throughput function determination…A variety of chemically derivatized slides…can be printed[,] for example slides treated with aldehyde-containing silane reagent. These aldehydes can react readily with primary amines on the proteins…" (Office Action mailed January 21, 2009, p. 7) and that MacBeath "teaches a method for analyzing interaction between a reactive protein and the substrate peptide…" as claimed in

claim 6.

However, as acknowledged by the examiner, "MacBeath is silent on teaching that the substrate peptide is immobilized on the solid substrate by the mediation of a linker protein." (Office Action mailed August 17, 2009, p. 9.) MacBeath does not provide a substrate peptide so attached by a linker to a solid substrate.

The examiner cites Inglese as "teach[ing] fusion protein with a substrate protein fused to a linker protein…it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ the reagents of Inglese, which includes proteins linked to substrate peptides, in the protein microarray of MacBeath in order to immobilize small substrate peptides." (Office Action mailed August 17, 2009, p. 9.) Applicants respectfully disagree.

Specifically, the examiner points to Inglese's use of leptin and applicants' recitation of leptin as an option for the linker protein "L" of the claimed chip. It is noted that where "L" is leptin, then applicants' claim 1 will provide a protein chip of S-leptin-SP form. The combination of MacBeath and Inglese does not teach a protein chip of S-leptin-SP form.

In the claimed invention, the linker is used to increase the efficiency of analysis of a substrate peptide by linking the substrate peptide, which is a target protein for analyzing, to a solid substrate. The linker is not a target protein for analyzing. In the present invention, leptin is not a target for analyzing.

By contrast, in Inglese, leptin IS a target compound for analyzing. As provided in the Abstract of Inglese, the A-B-C structure of Inglese is a reagent for introducing phosphorylation sites into a compound in order to label the compound with ^{33}P (*See* exemplary Fig. 2B and col. 9, line 56 to col. 10, line 5).

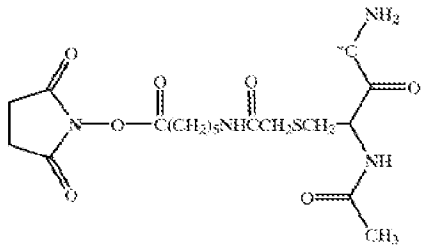
In the examples provided at col. 13, lines 26-51, a leptin-peptide A conjugate and a leptin-[$^{33}PO_3$]peptide A conjugate are provided. However it is noted that leptin is the target of detection for confirming introduction of a phosphorylation site using SDS-PAGE (col. 10, lines 7-8; col. 13, lines 26-51). Leptin is not used for increasing analysis efficiency in Inglese. Accordingly, Inglese does not provide a linker (L) as recited in claim 1.

In *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court reaffirmed the

principle that a factfinder judging patentability "should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." This prohibition against the use of hindsight is particularly apposite in the present circumstance. In view of the teaching of MacBeath and the teaching of Inglese, one of skill in the art would not have been led or in any way motivated to combine the array of MacBeath with a leptin-containing conjugate of Inglese with any reasonable expectation that a chip with increased efficiency for analysis of a substrate peptide would be produced.

Furthermore, the examiner alleged that "it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the reagents of Inglese, which includes proteins linked to substrate peptides, in the protein microarray of MacBeath."

For clarification, it is noted that the leptin-peptide A and leptin-[$^{33}PO_3$]peptide A conjugates are NOT the A-B-C reagents described in Inglese but are "conjugates of the reagent" that are prepared, purified and characterized. An example of the reagent is seen in claim 6 of Inglese, "said reagent comprising the structure A-B-C wherein A is an N-hydroxysuccinimide ester, B is a linking group, and C is a peptide sequence that comprises a kinase substrate." Examples of B are provided at col. 4, lines 7-62. One example of the reagent A-B-C, as provided in claim 8 is:



The inventors of the claimed invention recognized the problem that when the low molecular weight substrate peptide was immobilized on the protein chip, its interaction with the antibody did not occur. The examiner's attention is respectfully drawn to the examples provided in the specification of applicants' application, showing that when only the substrate peptide such as the low molecular weight kemptide was immobilized on the protein chip, its interaction with the antibody did not occur, but that when the peptide in a form fused with the linker protein such as leptin or malic enzyme was immobilized, its specific interaction with the antibody occurred. Such a problem was not recognized prior to the present invention and therefore one of skill would not have been motivated to solve such problem.

In considering a reference for its effect on patentability, the reference is required to be considered in its entirety, including portions of teach away from the invention under consideration (MPEP §2141.02). In *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court further confirmed that references that teach away from the invention are evidence of the non-obviousness of a claimed invention.

The cited MacBeath and Inglese references recognize problems in the art that differ from the problem addressed by the chip of applicants' claimed invention and therefore these references teach away from finding such a solution.

The array of MacBeath was developed to address the problem of the inability to use aldehyde slides when "peptides or very small proteins are printed" and to address the related obscuring of molecules of interest by BSA. (MacBeath, paragraph bridging p. 1760-1761).

The objective of Inglese is to provide a method to chemically modify already existing proteins and peptides so that they become substrates for protein kinase. ("The present invention relates to methods and reagents for introducing a substrate for a kinase into a compound, and for phosphorylating the resulting product." (Inglese, col. 3, lines 35-37.)) Namely, Inglese teaches a method that allows introduction of phosphorlyation site in a protein in order to label the protein with ^{32}P. ("A reagent is described for incorporating phosphorylation sites into compounds" Inglese, Abstract.)

Due to the different objectives between Inglese and MacBeath, it cannot be expected that one skilled in the art would have employed the reagents of Inglese in the array of MacBeath in order to address the issue of BSA obscuring molecules of interest.

Still further, the examiner states that the array of MacBeath provides "an ideal system… for the rapid and parallel identification of substrates of protein kinases using protein microarray spotted with protein substrates such as kemptide." (Office Action mailed August 17, 2009, p. 9.)

However, a method for preparing the microarray of MacBeath is different from the present invention. The protein microarray of MacBeath requires complex chemical treatments for an introduction of an aldehyde functional group on a surface of the chip. Also, it is manufactured by a Schiff's base combination with an amine group on peptide, and MacBeath merely identifies a kinase activity as a HTS form using such protein microarray. While MacBeath alleges that

"specific binding could be detected using Cy5-FKBP12 concentrations as low as 150 pg/ml" (p. 1761, 3rd col.), the present invention can measure the kinase activity even with **1.5 pg**. (*See* p. 315 of Lee et al., *Anal. Biochem.*, 330:311, 2004 provided by IDS herewith. The authors of this reference are the present inventors.) The detection efficiency of the present invention is thus improved a hundred-fold over that of MacBeath. Accordingly, the claimed chip of the present invention provides a marked improvement over the results achieved with an array of MacBeath.

MacBeath in view of Inglese fails to provide any derivative basis for the claimed invention. Additionally, there would have been no logical reason for one of skill in the art to combine such references. Accordingly, no basis of *prima facie* obviousness of the claimed invention is presented by such cited references.

Based on the foregoing, MacBeath in view of Inglese does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1 and 4-6 under 35 U.S.C. § 103(a) as being obvious over MacBeath in light of Inglese is respectfully requested.

Additionally, in the Office Action mailed August 17, 2009 the examiner raised a new ground of rejection with regard to claims 7 and 9 under 35 U.S.C. §103(a) as unpatentable over MacBeath in view of Inglese and further in view of U.S. Patent Application Publication No. 2002/0028463 (hereinafter "Duffy"). Applicants respectfully disagree.

Claims 7 and 9 are both of dependent form from claim 1. It is well established that if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). (MPEP §2143.03). As set forth in detail above, claim 1 is nonobvious over MacBeath in light of Inglese.

The examiner cites Duffy as "teach[ing] a protein chip of a S-L-SP form…wherein the reactive protein is an antibody labeled with fluorescent tags." (Office Action mailed August 17, 2009, p. 7). However, Duffy relates to an array system that facilitates the simultaneous monitoring of interactions between biological molecules, and merely suggests a bond between streptavidin and biotin as one of methods for modifying a surface of array. Duffy does not remedy the deficiencies of the combination of MacBeath and Inglese as set forth in detail above.

MacBeath and Inglese in view of Duffy does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 7 and 9 under 35 U.S.C. § 103 (a) as being

obvious over MacBeath in view of Inglese and further in view of Duffy is respectfully requested.

CONCLUSION

Based on the foregoing, all of applicants' pending claims 1, 4-7, 9, 11 and 12 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the August 17, 2009 Office Action without extension was set at three months, or November 17, 2009. Applicants hereby request a one month extension of time under 37 C.F.R. § 1.136 to extend the deadline for response to and including December 17, 2009.

Payment of the extension fee of $65.00 specified in 37 C.F.R. § 1.17(a)(1) and the RCE fee of $405.00 specified in 37 C.F.R. § 1.17(e), as applicable to small entity, is being made by on-line credit card authorization at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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